REMARKS

Claims 1-8, 13, 14, 17-20, and 22-25 are pending. Claims 1, 2, 13, 15, 19-21 and 23 are amended. Claims 9-12 were previously cancelled.

The Final Office Action mailed on January 8, 2004, rejected claims 1-8, 13, 14, 17-20, and 22-25 under 35 U.S.C. §112, first paragraph for lack of enablement, and under 35 U.S.C. §102(e) and 103(a) as being either anticipated by or obvious in view of Hiserodt et al., (U.S. 6,277,368). These rejections were maintained by the Examiner in view of Applicant's Appeal Brief submitted on June 25, 2004. The Examiner contends that the recitation of the term "vaccinate" requires that the methods of the invention result in the prevention or protection against a particular disease, and further asserts that Hiserodt et al. teach cytokine coated cells comprising exogenous cytokine. Applicant has rebutted these rejections in the Appeal Brief of June 25, 2004, but Applicant's arguments set forth therein appear to have been, on the whole, not considered, given that the Examiner's Answer, mailed on August 11, 2004, does not address a majority of Applicant's arguments from the Appeal Brief.

Applicant responded to the Final Office Action on March 25, 2004, and submitted therewith a second Rule 132 Declaration. As noted in MPEP 706.07(h), on filing an RCE, Applicant may direct that the previously filed, but un-entered After-final amendment, response and 132 Declaration not be entered, but that, instead, the present submission and 132 Declaration submitted herewith be entered for consideration by the Examiner. Accordingly, Applicant requests that the previously filed After-final amendment and Rule 132 Declaration ("the second Segal Declaration") not be entered into the file, but that instead, the Examiner enter the instant submission and Rule 132 Declaration.

Without acquiescing to the Examiner's rejections, and solely for the purpose of expediting prosecution, Applicant has amended the claims to delete all reference to "vaccinate" or "vaccine" and instead recite "A method for stimulating an immune response in a mammal...". Support for this amendment is found throughout the specification, for example, on page 9, line 21 through page 10, line 2. For example, the specification teaches that an immune response is stimulated when the response is at least 5% greater as compared to an immune response in the

absence of the administered compositions recited in the claims. Thus, the amended language is both supported by the specification, and recites a clear and unambiguous endpoint for the claimed method.

Rejection of Claims 1-8, 13, 14, 17-20, and 22-25 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected the claims as not being enabled for "*vaccinating* a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any* cytokine coated cell comprising said antigen". Applicants respectfully disagree, however, in order to advance the prosecution of this application, Applicants have amended the claims to delete reference to "vaccination" and recite instead "stimulating an immune response".

The claims are enabled for stimulating an immune response

Applicant submits that the teachings of the specification provide a disclosure which is more than sufficient to permit one of skill in the art to practice the claimed invention without undue experimentation. The working example provided in the specification demonstrates a reduction in tumor formation which exemplifies the claim requirement of "stimulating an immune response". The specification teaches that stimulating of an immune response may be evidenced by an assay for tumor rejection in which "if survival or tumor onset in these animals [to which has been administered a cytokine-coated cell of the invention] differs from that of [an] animal vaccinated, using identical parameters, with irradiated non-cytokine coated cells...immunomodulation has occurred" (page 90, lines 25-27). Accordingly, Example 7 teaches that after administration of cytokine-coated (GM-CSF-GPI-coated) B16 cells, mice (n=5) had a maximum survival period of 32 days. In contrast, control mice (n=4; administered the B16 cells in the absence of GM-CSF-GPI) had a mean survival time of 16 days. As described above, the specification teaches that the immune stimulating is deemed successful where the response is stimulated/activated by about at least 5% as compared to an immune response in the absence of the cytokine coated cell as recited in the claims (p. 10, lines 19-24).

The Examples in the specification, in addition to the post-filing declarations filed by Applicant under 37 C.F.R. §1.132 provide six different working examples of stimulating of an

immune response in a mammal using the methods described in the specification. As shown in Example 7, 20% of the test group had a survival time which was 100% greater than the mean survival of the control group (1 animal in 5 (i.e., 20%) had a 32 day survival time relative to the mean 16 day survival time in controls). In addition, Example 8 in the specification, although prophetic, teaches stimulation of an immune response in mice with cytokine coated cells wherein at day 60 after the challenge step, "at least 20% or more of the mice that received GPI-GM-CSF coated cells will be alive as compared to control mice". The Rule 132 Declaration filed by Dr. Andrew Segal on February 28, 2003 ("the first Segal declaration") gives a working example of the method described in Example 8. The first Segal declaration teaches that of mice administered GM-CSF-GPI cytokine coated cells (fibrosarcoma cells), 60-80% of the mice did not show development of tumors for 70 days. That is, the cytokine coated cell composition of the invention stimulated an immune response and prevented tumor formation in 60-80% of treated animals.

Applicant also submitted a second Rule 132 Declaration by Dr. Andrew Segal ("the Second Segal declaration") with the Amendment After Final Rejection. This Declaration was not entered, however. Applicant are submitting a revised version of the Second Segal declaration herewith, with correction of minor typographical errors and additional data (discussed in detail below). MPEP §706.07(h) stipulates that Applicant, on filing an RCE, can specifically instruct the Patent Office not to enter a previously filed, but un-entered after-final amendment and Declaration, but to instead enter the present amendment and Declaration. Applicants, accordingly, request that claim amendments, remarks, and the Second Segal Rule 132 Declaration filed herewith be entered in place of the Amendment after final and Second Segal Declaration filed on March 25, 2004. The second Segal declaration demonstrates that 100% of mice which received GM-CSF-HA-coated CMS-5 fibrosarcoma cells were tumor-free after 40 days, compared to control animals who developed tumors by day 18. That is, the vaccine composition stimulated an immune response, thereby preventing tumor growth, in all animals to which it was administered. The second Segal declaration also shows that of mice administered K1735 melanoma cells coated with GM-CSF-HA, 70% were tumor free after more than two months, whereas all control animals had developed tumors in the same time period. That is, the vaccine composition stimulated an immune response in 70% of animals to which it

was administered. The second Segal declaration also shows that in mice administered B16F10 murine melanoma cells coated with GM-CSF, an average of 97.5% of metastases to the lungs of the test animals were prevented, thus evidencing the stimulation of an immune response. Similarly, the second Segal declaration shows that lung metastases in a CT26 murine colon carcinoma model were reduced by approximately 45% following administration of GM-CSF coated CT26 cells. That is, the method of the invention prevented 45% of lung carcinoma metastases compared to control. In addition, the second Segal declaration shows that the ability of administration of GM-CSF coated CT26 cells to prevent lung metastasis was reduced in mice which had been depleted of either CD4+ or CD8+ T cells. The second Segal declaration also shows that cytokine coated CMS5 fibrosarcoma cells stimulated an immune response in the host animal to which they were administered as evidenced by the lack of immune stimulation in host animals which had been depleted of either CD4+ or CD8+ T cells.

Importantly, the Second Segal Declaration demonstrates that **the administered composition (i.e., a cytokine coated cell) acted through stimulation of an immune response**. *In* vivo depletion of T cell subsets showed that the anti-tumor effect (anti-tumor effect on both primary tumors and metastatic tumors) of the cytokine coated cells comprising the exogenous cytokine was dependent on the presence of CD4+ and CD8+ T cells. It is well known in the art that CD4+ and CD8+ T cells are the key effectors of antigen-specific cellular immune responses. See, e.g., Janeway et al., 1999, Immunobiology, Garland Publishing NY, NY.

Moreover, the Second Segal Declaration presents data from an ELISPOT assay that directly demonstrates that administration of cytokine-coated tumor cells comprising an exogenous cell-bound cytokine elicits a marked increase in tumor-antigen specific gamma-interferon secreting T cells, compared with administration of tumor cells alone or tumor cells mixed with regular GM-CSF, which cannot bind to the cells to form cytokine-coated cells. This data clearly shows that the teachings in the specification permit one of skill in the art to practice the invention with no more than routine experimentation.

With respect to the Examiner's assertion that the claims are not enabled for vaccinating a mammal to *any* antigen, comprising administering to a mammal *any* vaccine comprising *any*

cytokine coated cell comprising said antigen, the Examiner has previously acknowledged that the specification provided a list of cytokines which would function to bring the cytokine coated cell into contact with a leukocyte. As noted above, the instant claims have been amended to recite a method for stimulating an immune response, rather than a method for vaccinating. To the extent that the rejection is maintained against the amended claims, Applicant provides the following remarks.

The specification is enabled for stimulation of an immune response against antigen

The Examiner has maintained that the specification was not enabled for *any* antigen, particularly in view of the teachings of several publications which reflected the state of the art which existed years prior to Applicant's invention, and which suggested that vaccination of the type claimed was unpredictable (The Examiner cites Ellis (Chapter 29 of Vaccines), Chandrasheker et al. (U.S. Pat. No. 6,248,329), Spitler (Cancer Biotherapy), and Ezzell (NIH Research), all of which were discussed in Applicant's response of October 22, 2003). The Examiner asserts that the specification is not enabled for vaccination against *any* antigen using the cytokine-coated cells of the invention. Applicants respectfully disagree with the Examiner.

Applicant submits that an antigen, by definition, is capable of eliciting an immune response (See, e.g., specification, p. 14, lines 4-5) Applicant also submits that the immune response to an antigen generally arises from the same set of mechanisms, regardless of the origin of the antigen. Thus, for example, immune responses to the MAGE-1 melanoma tumor antigen, the herpes simplex glycoprotein D viral antigen, and the diptheria toxoid bacterial antigen all result from uptake of the respective antigen by antigen presenting cells, intracellular processing of the respective antigens into short peptides, and presentation of these peptides by APCs to T cells, with activation and expansion of these T cells (See, e.g., Immunobiology: The Immune System in Health and Disease by Janeway & Travers 1997, Elsevier Science Ltd./Garland Publishing, New York; p. 272-277). Applicant therefore submits that the state of the art supports the expectation that if one or several antigens are operative according to the invention, that many will be, thereby providing enablement for the full scope of the claims. Applicant submits that, in the specification and the First and Second Segal Declarations, they have provided evidence that

the invention is operative for at least six different types of antigens, viz. antigens of CMS-5, B16, and CT26 tumor cells, ovalbumin, and B16-specific antigens gp100 and TRP-2, and thus provides enablement sufficient to support the full scope of the claimed invention.

Furthermore, in the Second Segal Declaration filed herewith, Applicant presents data demonstrating that the claimed invention is operative for the antigen ovalbumin. Ovalbumin is a "test antigen" used by those skilled in the art as a generic antigen representative of antigens in general. Data in this Declaration also demonstrates stimulation of immune responses to the antigens gp100 and TRP-2. Thus, Applicant has documented that the invention as claimed is operative for a number of antigens, including both tumor and non-tumor antigens.

As Applicant described in the November 5, 2003 telephone interview, one advantage of the present invention is that upon administration of the composition of the invention to a mammal, the mammal's immune system is presented with **all** of the potential antigens which are present in or on the cytokine coated cell. It is thus not necessary that one of skill in the art know the specific antigens present in the cell (i.e., which epitope of the cytokine coated cell composition the mammal is reacting to) in order to successfully practice the invention. The invention therefore also provides an opportunity to elicit an immune response against multiple antigens in a cell, regardless of whether the identity of any of those antigens is known. Furthermore, whole cells may be used as a substrate in assays to determine whether an immune response to an antigen contained in the cells has been stimulated, so that the identity of a specific antigen need not be known in order to demonstrate the successful practice of the invention. Indeed, such a method was used in the ELISPOT assay presented in the Second Segal Declaration.

Applicant also respectfully submits that Examiner's previously stated concerns regarding enablement of protection against disease do not apply to the claims as currently amended.

The specification provides sufficient enabling disclosure

Applicant submits that to satisfy the enablement requirement, the specification must provide sufficient teaching to permit one of skill in the art to practice the invention without

undue experimentation, and can include teachings which permit one of skill in the art to make a determination of whether a specific species of the invention is operable, without undue experimentation. Applicant asserts, at the outset, that the specification and the examples teach the general procedures required to practice the invention, as well as specific, step-by-step descriptions of the practice of the invention. The Examiner asserts that the specification is not enabling for each and every possible embodiment of the invention as previously claimed (e.g., the Examiner asserts that all antigens derived from pathogens may not be successful in protecting a mammal from disease, which is in any case not pertinent to the currently amended claims). To the extent that the Examiner maintains this rejection against the currently amended claims, Applicant submits that this is irrelevant under established, governing law. **Lack of a detailed description for each and every embodiment of the invention does not render the claimed invention non-enabled.** Applicant respectfully refers the Examiner to *Ex parte Mark* (12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989). In this case, the broadest appealed claim was as follows:

> 1. A synthetic mutein of a biologically active native protein in which the native protein has at least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

Id., at 1905. The claim in *Mark* thus covers a mutant protein containing an amino acid that has been substituted for a non-essential cysteine residue. The specification at issue in that case set forth three working examples in which it was shown that each of three proteins had a non-essential cysteine residue which could be deleted or replaced, with retention of biological activity in the resulting mutein.

The Examiner in *Mark* raised two overbreadth issues with respect to this claim: (1) whether the specification supported a claim broad enough to encompass any mutant protein and (2) whether the specification supported a claim broad enough to encompass substitution of any cysteine residue within the protein. The Examiner's reasons for rejecting the broad claim in *Mark* were as follows:

> Essentially, the position taken in the rejection is that it would require undue further experimentation to construct by recombinant methods (site specific mutagenesis) the innumerable muteins encompassed by the instant claims (claims encompass modification of any protein which comprises a "non-essential" cysteine residue) and to screen the muteins produced for any of those which exhibit biological activity after modification.

Id., at 1906. The Examiner also stated that the claims were broad enough to "encompass any protein, even those which have not been characterized or cloned." *Id.*, at 1906.

The Board of Appeals disagreed with the Examiner's analysis and concluded that the claim was enabled for all cysteine-depleted muteins of biologically active proteins in which the mutein retains the biological activity of the native protein. The Board reframed the enablement issue and reasoned that the record established that, for a given protein having cysteine residues, one skilled in the art 1) would be able to substitute for or delete the cysteine residues as desired, and 2) could routinely determine whether deletion or replacement of cysteine residues in a given instance in fact resulted in an operative mutein falling within the claims. Upon applying this framework to the specification and claims before them, the Board concluded that, although some cysteine-depleted muteins may not be operable, the disclosure was enabling for the claims, since one skilled in the art was (1) clearly enabled to perform the work that was needed to produce any given mutein falling within the description in the claims and (2) to determine whether the cysteine depleted construct retained the biological activity of the native protein.

Applying the rational of the Board in *Mark*, Applicant submits that the specification has provided sufficient teachings to enable one of skill in the art to make and use the claimed invention without undue experimentation. Given the claims of the present invention, the specification must teach one of skill in the art how to make a composition comprising a cytokine coated cell according to the invention, including a description of the cytokines and antigens to be included in the composition. The specification must also teach what types of cells may be used to produce the composition, and how to administer them to a mammal. Lastly, the specification must teach how one of skill in the art would determine whether an immune response is stimulated in a mammal to which the composition is administered. In fact, the specification teaches the following.

1. The specification teaches on pages 16-47, more than six different families of cytokines useful in the invention, including over 80 specifically referenced cytokine molecules which may be used in vaccine compositions of the invention. These teachings include discussions of the roles of these cytokines in the immune response.

2. The specification teaches at pages 68-71, that antigens useful in the methods of the invention include **viral antigens** including hepatitis viral antigens e.g., hepatitis A, B. and C, viral components such as hepatitis C viral RNA; influenza viral antigens such as hemagglutinin and neuraminidase and other influenza viral components; measles viral antigens such as the measles virus fusion protein and other measles virus components; rubella viral antigens such as proteins E1 and E2 and other rubella virus components; rotaviral antigens such as VP7sc and other rotaviral components; cytomegaloviral antigens such as envelope glycoprotein B and other cytomegaloviral antigen components; respiratory syncytial viral antigens such as the RSV fusion protein, the M2 protein and other respiratory syncytial viral antigen components; herpes simplex viral antigens such as immediate early proteins, glycoprotein D, and other herpes simplex viral antigen components; varicella zoster viral antigens such as gpI, gpII, and other varicella zoster viral antigen components; Japanese encephalitis viral antigens such as proteins E, M-E, M-E-NS 1, NS 1, NS 1 -NS2A, 80%E, and other Japanese encephalitis viral antigen components; rabies viral antigens such as rabies glycoprotein, rabies nucleoprotein and other rabies viral antigen components; **bacterial antigens**, including pertussis bacterial antigens such as pertussis toxin, filamentous hemagglutinin, pertactin, FIM2, FIM3, adenylate cyclase and other pertussis bacterial antigen components; diptheria bacterial antigens such as diptheria toxin or toxoid and other diphtheria bacterial antigen components; tetanus bacterial antigens such as tetanus toxin or toxoid and other tetanus bacterial antigen components; streptococcal bacterial antigens such as M proteins and other streptococcal bacterial antigen components; gram- negative bacilli bacterial antigens such as lipopolysaccharides and other gram-negative bacterial antigen components; Mycobacterium tuberculosis bacterial antigens such as mycolic acid, heat shock protein 65 (HSP65), the 30kDa major secreted protein, antigen 85A and other mycobacterial antigen components; Helicobacter pylori bacterial antigen components; pneumococcal bacterial antigens such as pneumolysin, pneumococcal capsular polysaccharides and other pneumococcal bacterial antigen components; hemophilus influenza bacterial antigens such as capsular polysaccharides

and other hemophilus influenza bacterial antigen components; anthrax bacterial antigens such as anthrax protective antigen and other anthrax bacterial antigen components; rickettsiae bacterial antigens such as romps and other rickettsiae bacterial antigen component; **fungal antigens** such as candida fungal antigen components; histoplasma fungal antigens such as heat shock protein 60 (HSP60) and other histoplasma fungal antigen components; cryptococcal fungal antigens such as capsular polysaccharides and other cryptococcal fungal antigen components; coccidiodes fungal antigens such as spherule antigens and other coccidiodes fungal antigen components; and tinea fungal antigens such as trichophytin and other coccidiodes fungal antigen components; **parasite antigens** such as plasmodium falciparum antigens such as merozoite surface antigens, sporozoite surface antigens, circumsporozoite antigens, gametocyte/gamete surface antigens, blood-stage antigen pf 1 55/RESA and other plasmodial antigen components; toxoplasma antigens such as SAG-1, p30 and other toxoplasma antigen components; schistosomae antigens such as glutathione-S-transferase, paramyosin, and other schistosomal antigen components; leishmania major and other leishmaniae antigens such as gp63, lipophosphoglycan and its associated protein and other leishmanial antigen components; and trypanosoma cruzi antigens such as the 75-77kDa antigen, the 56kDa antigen and other trypanosomal antigen components; and **tumor antigens** such as telomerase components; multidrug resistance proteins such as P-glycoprotein; MAGE-1, alpha fetoprotein, carcinoembryonic antigen, mutant p53, papillomavirus antigens, gangliosides or other carbohydrate-containing components of melanoma or other tumor cells.

3. The specification teaches at page 71 to 76, methods for expressing nucleic acid molecules encoding antigens of the invention in a host cell. The specification also teaches at page 78, lines 3-6 that a cell of the invention may already express a target antigen, and therefore need not be made to express the antigen.

4. The specification teaches at page 76-77, multiple cell types which may be used according to the invention to generate cytokine-coated cells.

5. The specification teaches at page 104-107, methods for administering the vaccine of the invention to a mammal, including methods for preparing pharmaceutical formulations, dosages, and routes of administration.

6. The specification teaches at page 82-89, **methods for determining whether an immune response has been stimulated in an animal**. Specifically, the specification teaches that stimulation of an immune response may be determined by assays for antigen-induced T cell proliferation, assays for lymphokine-dependent cell proliferation, [^{3}H]thymidine pulse and harvest of cell cultures, immuno-enzymatic assays for cytokines using NIP- and HRPO-labeled antibodies, measuring induction of *in vivo* antibody responses to protein/polysaccharide antigens, and assays using tumor rejection. With respect to determining stimulation of an immune response based on tumor rejection, the specification teaches that if survival or tumor onset in animals to which have been administered a vaccine of the invention differs from that of a control animal, then immunostimulation has been achieved.

Thus, under established law, the specification provides more than ample guidance to one of skill in the art to practice the invention according to the full scope of the claims. The specification teaches how to utilize a cytokine according to the methods of the invention and methods for determining the effectiveness of the methods of the invention. The individual methodologies, cytokines, and molecular biological techniques described in the application for use in practicing the invention are routine in the art. Accordingly, Applicant's teachings of the specific types of molecules to be used according to the invention, the fact that **the claimed method administers all of the antigens present in a cytokine coated cell to a mammal**, and the teachings of specific routine assays to determine whether an immune response is stimulated in a mammal by the method of the invention, all provide sufficient disclosure to permit one of skill in the art to practice the invention without undue experimentation.

Applicant further notes that, under established law, the existence of non-operative embodiments of the claims does not impair the invention's patentability. The courts have long held that non-operative embodiments are permissible, and are not fatal to a finding of enablement. See, eg., *Atlas Powder Co. v. E.I. du Pont de Nemours &Co*, 750 F.2d 1596 (Fed. Cir. 1984) (holding that the presence of inoperative embodiments does not necessarily render a claim nonenabled).

Testing is not undue experimentation

The Examiner has asserted that it would be undue experimentation for one of skill in the art to have to test different cytokines and cell types to determine which combination would make an effective composition for stimulating an immune response for a particular application. Applicants submit that the legal standard on which the enablement requirement is based hinges on a determination of whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation, not whether testing is required to practice the full scope of the claimed invention. As stated in *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ 2d 1217 (Fed. Cir. 1988), *cert denied*, 490 U.S. 1046 (1989), the court reversed the findings of the district court of undue experimentation where the specification provided only one working example. "The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and cost of such studies...failed to show undue experimentation." MPEP 2164.06 further points to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 217-19 (CCPA 1976)), which states:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicants submit that the present specification described in detail not only one, but many working embodiments of the invention which fall under the claims, and thus, like the patent at issue in *United States v. Telectronics, Inc., supra*, is enabling and should not be subject to the Examiner's rejection.

Applicant further submits that the specification goes beyond the minimal enablement requirement, and provides broadly applicable methods for determining whether any specific embodiment would function to stimulate an immune response in a mammal according to the claimed invention. Furthermore, these methods (aside from the fully enabled steps of making and administering a cytokine-coated cell of the claims) are standard, workaday methods in the art and are therefore no more than routine.

Applicant also submits that in general, with respect to the amended claims drawn to "stimulating an immune response", the practitioner of the invention will already be in possession of the antigen(s) to which he or she desires to stimulate an immune response., e.g. in the form of cells containing the antigen(s). That is, the present invention provides a method for stimulating an immune response once cells comprising an antigen have been selected. The antigen, in the form of a cell bearing the antigen, will be selected by one of skill in the art, based on their reasons for desiring to stimulate the immune response. Thus, the selection of the antigen or cell to use with the method of the invention is left to the discretion of the practitioner, and for purposes of practicing the invention, the practitioner's motivation in selecting a particular antigen in the form of an antigen bearing cell is irrelevant. The present invention provides the method by which the skilled practitioner can then utilize their selected antigen-bearing cell to stimulate an immune response. Applicant also reiterates, as discussed above, that operativity with respect to one (or in this case actually several) antigens in combination with a given cytokine indicates operativity for a wide range of antigens in combination with the same cytokine, since the immune system uses the same mechanisms to process antigens from disparate sources.

To reject the claims for lack of enablement, the Examiner must make specific findings of fact, supported by the evidence, as to why one of skill in the art would not be able to practice the invention, given the extensive teachings provided by Applicant, without undue experimentation. MPEP 2164.04. In addition, the Examiner is required to provide specific technical reasons why undue experimentation would be required to practice the invention. Id. Applicant submits that, other than stating that undue experimentation would be required to practice the invention, *the Examiner has not pointed out any technical, or factual reasons why this would be the case.*

Predictability

In the Examiner's Answer to Applicant's appeal brief, the Examiner sets out an argument that the prior art (several of which were published as much as ten years prior to the earliest filing date of the present application) teaches that the claimed invention would be unpredictable. The

references cited by the Examiner are all drawn to vaccination of an animal. The claims, however, have been amended to recite "stimulation of an immune response", and thus the Examiner's assertions with respect to predictability are moot. Nevertheless, Applicant respectfully requests that the Examiner consider the following remarks and, if the Examiner still concludes that the cited references evidence unpredictability of the claimed invention, that the Examiner explain the basis for finding Applicant's remarks unpersuasive.

The Examiner asserts that it is "well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity". Applicant respectfully submits that the instant claims are drawn to stimulation of an immune response and that Examiner's objection therefore has no bearing on these claims. To the extent that the Examiner maintains this rejection against the claims as currently amended, Applicant requests consideration of the following remarks: The Examiner asserts that Ellis (Chapter 29 of Vaccines, published **seven years** before Applicant's filing date) "exemplifies this problem" in the recitation that "The key to the problem is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies...and thus protect the host against attack by the pathogen". Applicant submits that the quoted phrase is used in the context of describing the development of a recombinant DNA based vaccine. The present invention is designed to target an *antigen bearing cell* to a leukocyte by attaching exogenous cytokine molecules to the cell. Accordingly, **the invention does not require that a specific antigen be identified**; indeed, the invention provides a method by which **every antigen in the cell is targeted to immune cells**, and thus offered to the host's immune system. Thus, **there is no "problem" of antigen selection to overcome**. The invention provides the immune system with all the antigens present in the cytokine coated cell against which to mount an immune response and eradicate the antigen bearing cells; this occurs without the need for the practitioner to know precisely what antigen present in the cytokine coated cell will trigger the immune response.

The Examiner also cites Chandrasheker et al. (U.S. Pat. No. 6,248,329), asserting that the '329 patent teaches that it is understood in the art that the ability of antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune

response capable of protecting an animal from a specific disease, "associated with the antigen". Applicant submits, however, that this teaching is provided in the context of parasitic helminths. Specifically, the Examiner has omitted the final phrase of the relevant passage of the '329 patent which recites "associated with the antigen, *particularly in the case of parasitic helminths*". Thus, the 'unpredictability' purported to be taught by the '329 patent is restricted to stimulation of an immune response with antigen from one particular organism, in an attempt to stimulate immunity against one particular type of infection. In addition, the '329 states that "the ability of an antigen to stimulate antibody production does not *necessarily* correlate with the ability of the antigen to stimulate an immune response". In other words, the absence of an antibody response does not indicate the absence of any immune response; protection is often mediated by a cellular (T-cell) immune response. Such a response is taught in the instant specification, and is demonstrated in the Second Segal Declaration. Moreover, Applicant submits that the specification need not enable each and every potential embodiment of the invention., provided that the specification provides sufficient guidance to permit one of skill in the art to practice the invention without undue experimentation. See, eg., *Atlas Powder Co. v. E.I. du Pont de Nemours &Co*, 750 F.2d 1596 (Fed. Cir. 1984) (holding that **the presence of inoperative embodiments does not necessarily render a claim nonenabled**). Thus, even if one of skill in the art were to encounter difficulty in vaccinating a mammal against a parasitic helminth antigen, the specification provides sufficient guidance to permit one of skill in the art to determine whether such an embodiment would be operative or not, and thus the specification, as a whole, is enabling for the full breadth of the claimed invention. Moreover, as described above, the invention provides a method for providing all of the antigens in a cytokine coated cell of the invention to the immune system, in response to which the immune system can be stimulated.

The Examiner also cites Spitler (Cancer Biotherapy, published **three years** prior to Applicant's filing date), as speculating on the negative view an oncologist or venture capitalist would have of cancer vaccines if anyone were to bother to ask them. What the Examiner fails to point out, however, is that Spitler goes on to teach that "cancer vaccines have finally reached the stage in technological development where commercial development can be envisioned" (page 2, first full paragraph). Spitler notes that developing technology has permitted scientists to identify and characterize tumor associated antigens, determine their tissue distribution, and produce

virtually unlimited quantities of pure antigens for use in vaccine development (Id.). Interestingly, in contrast to the Examiner's assertion that vaccination against a particular antigen is insufficient to modulate disease, Spitler states that "[a]lmost everyone working in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy", and that "[i]nvestigators who have reported clinical successes with vaccine therapy in large series of patients include..." (citing Berd et al., *Ann NY Acad. Sci.* 1993, 690: 147; Bystryn, *Ann NY Acad Sci*, 1993, 690:190; Hersey et al., *Cancer Immunol Immunother*, 1986, 22:221; Mitchell et al., *Ann NY Acad Sci*, 1993, 153:666; Morto et al., *Ann NY Acad Sci*, 1993, 690:120; Seigler et al., *J. Biol Resp Modifiers* 1989, 1-16; Wallack et al., *Cancer*, 1986, 57:649). In contrast to the opening speculation as to the opinion of oncologists and venture capitalists, Spitler concludes by declaring, "[T]he decade of the vaccines may finally have arrived!". Moreover, the fact is that venture capitalists have, and had already as of Applicant's filing date, invested tens of millions of dollars in cancer vaccine companies such as CancerVax, Onyvax, Cell Genesys, Dendreon, and Antigenics. This establishes clearly that as of Applicant's filing date, the pessimism about cancer vaccines set out in Spitler was outdated, and no longer widely held.

The Examiner lastly cites Ezzell (NIH Research; published **four years** prior to Applicant's filing date); asserting that Ezzell teaches that "tumor cells simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes". Applicant submits that it is precisely an advantage of the present invention that it does not rely on the display of an antigen on the surface of a tumor cell for recognition by a T cell. Instead, the present invention provides a cytokine coated cell comprising the selected antigen (which need not be on the surface of the immunizing cell) and an exogenous cytokine which can bind to the surface of the immunizing cell. Without being bound to one particular theory, the invention is based, in part on the discovery that an exogenous cytokine on the surface of the immunizing cell will interact with a cell surface receptor on a leukocyte (including APCs such as dendritic cells), thus promoting engulfment and presentation of the antigen by the leukocyte, making presentation by the original antigen-bearing cell irrelevant. Thus, the antigen expression which is disfavored by Ezzell, i.e. expression by the tumor cell itself, has no bearing on the invention, which

provides an effective method (demonstrated by Applicant's teachings combined with the Dr. Segal's Rule 132 declarations) of stimulating an immune response in a mammal.

The Examiner asserts that Ezzell teaches that "no one is very optimistic that a single peptide or a virus carrying the gene encoding that peptide will trigger an immune response strong enough to eradicate tumors or even to prevent...later growth". Applicants assert again, however, that an advantage of the present invention is that it does not rely on the delivery of a "single peptide", but instead, presents a mammal to which the composition is administered **all of the antigens** present in a cytokine coated cell. Moreover, regardless of the outdated pessimism documented by Ezzell, Applicant has demonstrated that *the claimed invention works as taught*, and is capable of stimulating in a mammal an immune response to an antigen.

Accordingly, Applicant respectfully submits that the Examiner's assertion that the state of the art supports the conclusion that the present invention is unpredictable and/or inoperative is incorrect. Applicant submits that the specification provides extensive, detailed, and practical teaching as to the manner of making and using the claimed invention, and plural methods for determining whether an immune response is stimulated according to the invention, such that one of skill in the art could readily adapt the methods to a particular selected antigen of interest, and predict generally what the outcome would be.

Applicants assert that the claims are enabled commensurate with their scope and request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1, 2, 13, 14, 17-19, and 22-25 Under 35 U.S.C. §102(e)

Claims 1, 2, 13, 14, 17-19, and 22-25 stand rejected under 35 U.S.C. §102(e) as being anticipated by Hiserodt et al., U.S. Pat. No. 6,277,368 ("the `368 patent"). Applicant respectfully traverses the rejection.

It is the Examiner's position that the `368 patent teaches a method for vaccinating a mammal using a "composition comprising a cytokine coated cell comprising an exogenous cytokine," as claimed by the Applicant. Specifically, the Examiner states in the Final Office Action mailed January 8, 2004 as follows:

> [I]t is the examiner position, that US Patent '368 teaches a method of vaccinating a mammal, including mouse, to selected antigen, comprising administering a vaccine comprising a primary tumor cells and cytokine-secreting cells (see entire document, Abstract in particular). It is noted that "cytokine-coated cells" of the present invention are obtained by mixing cell[s] that already express an antigen, a tumor antigen for example, with engineered cytokines **that can become membrane-bound** (see page 79 lines 9-25 in particular). US Patent '368 teaches that cytokines secreted by said cytokine-secreting cells are exogenous to primary tumor cells (see column 7, lines 25-40 in particular).... (Final Office Action , page 5, lines 22-29; bold and underlined emphasis added)

At the outset, Applicants points out that the Examiner's reading of the present invention is not correct. "Cytokine-coated cells" of the invention are not cells mixed with cytokine "that **can** become membrane bound", but are cells mixed with cytokine which **is** membrane bound.

Applicant respectfully refers Examiner to the following language excerpted from claim 1 of the instant invention:

> ...administering to a mammal a composition comprising a cytokine-coated cell comprising said antigen, wherein said cytokine *of said cytokine-coated cell* is exogenous to said cell (italics added for emphasis).

Applicant also respectfully refers the Examiner to page 4, lines 13-16, of the instant specification which states that "cytokine-coated cells" are "cells which have been modified in such a manner as to bear a cell-surface associated cytokine" which "modulates the immune response in the recipient to a selected antigen or antigens contained in or attached to the [cytokine-coated] cells." Applicant also refers to the definition of "exogenous" on page 10 lines 28-29 of the specification as denoting something "introduced from or produced outside the cell." Therefore, taking the definitions of the specification along with the claim language, **the required elements of the claimed invention include the following:**

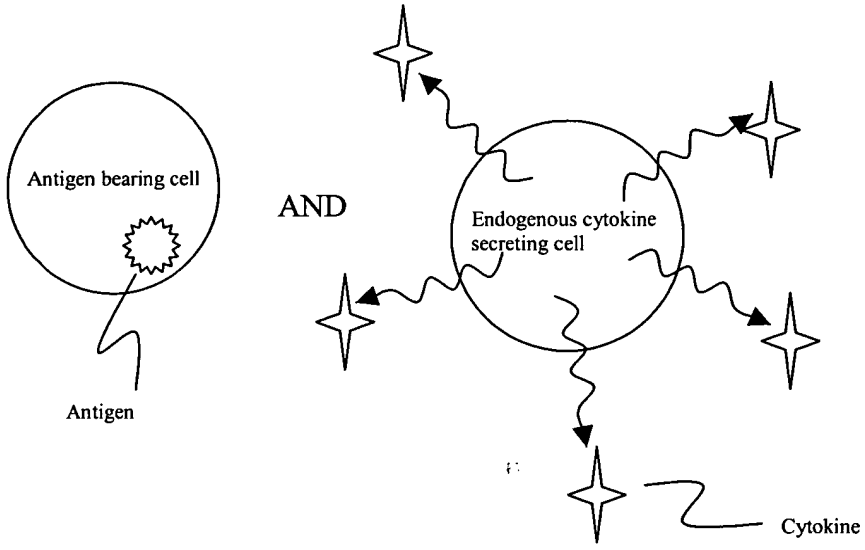
1) **An antigen-comprising cell having a cytokine attached to its surface, and**

2) **That the cytokine attached to that cell be exogenous *to that cell***

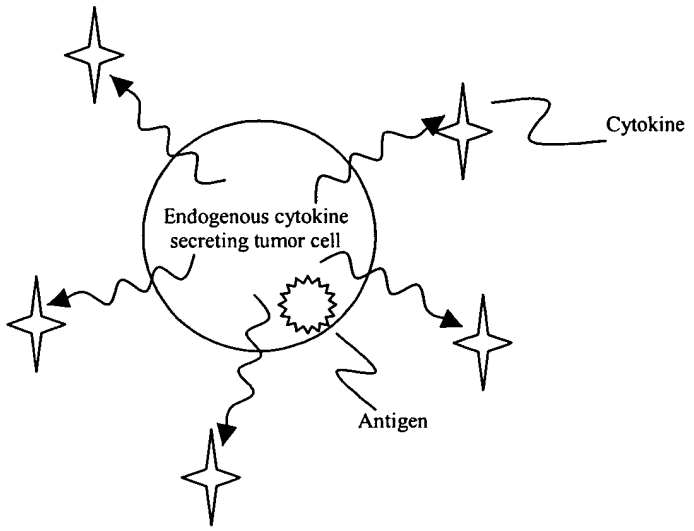
The '368 patent cited by the Examiner neither teaches nor suggests the combination of all of these elements, as required for a rejection under 35 U.S.C. §102(e).

More specifically, the teachings of the '368 patent are limited to:

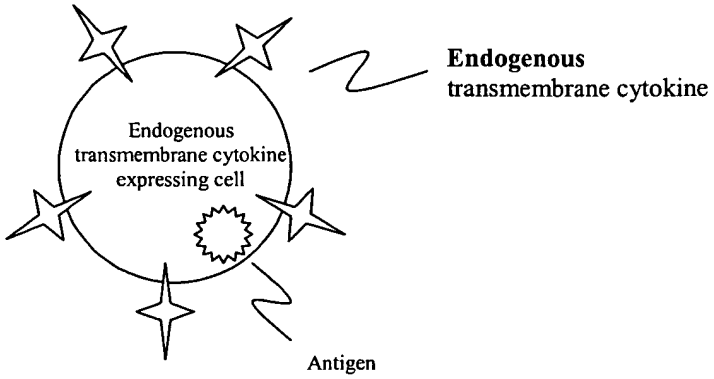
1. A first cell which comprises an antigen, and a second cell which secretes an endogenous cytokine (col. 7, lines 13-17; col. 15, lines 37-41); that is the cytokine is expressed from within the cell. No cytokine is attached to the surface of the antigen-containing cell; thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention.



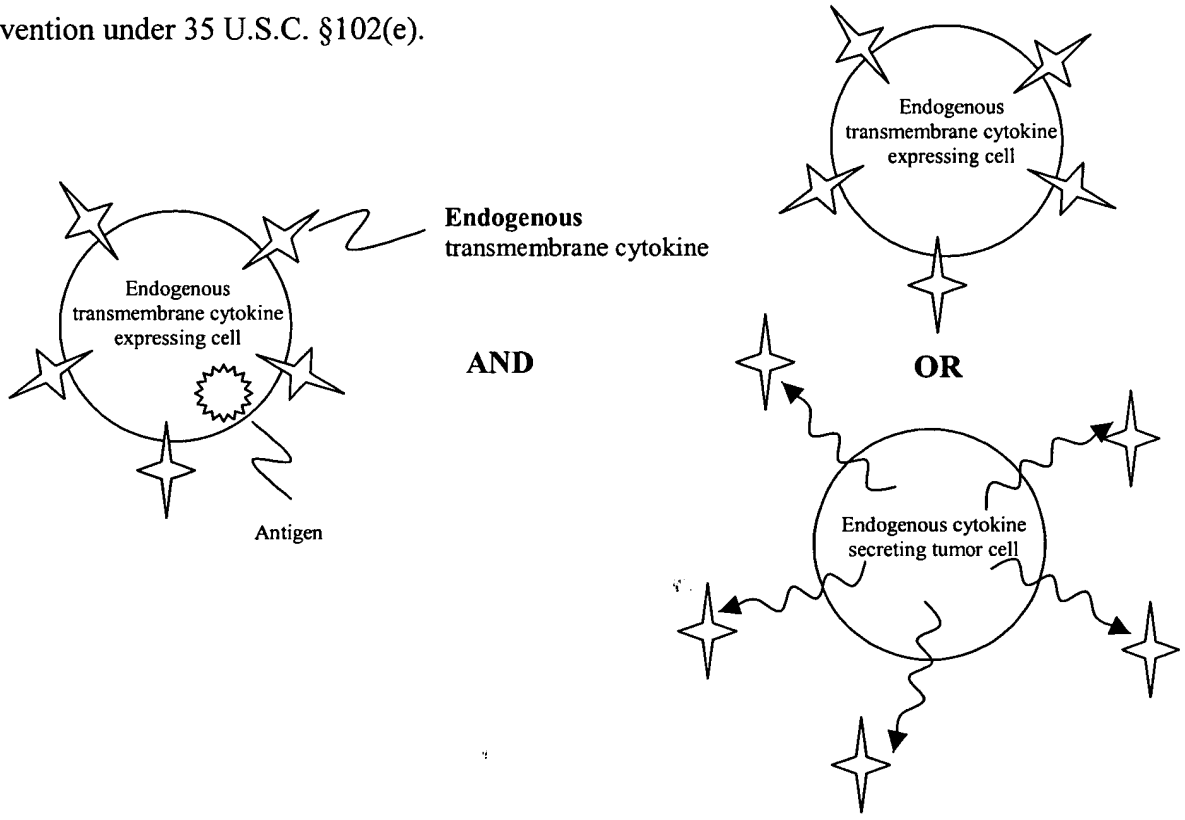
2. An antigen-containing cell that is genetically modified to secrete a soluble, endogenous cytokine (col.7, lines 21-26; col. 11, lines 30-34). Again, no cytokine is attached to the surface of the antigen-containing cell; thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention.



3. An antigen-containing cell that is genetically modified to express an endogenous, transmembrane cytokine (col. 16, lines 57-65). Here, a cytokine is attached to the surface of the antigen-containing cell, but it is ***endogenous*** to this cell, i.e. expressed from within, rather than ***exogenous*** to it. Although it may incidentally be exogenous to other antigen-containing cells in the composition, it is not both **attached** to **and** **exogenous** to the same cell, as expressly required in the instant claims. Thus, this embodiment of Hiserodt does not anticipate the instantly claimed invention under 35 U.S.C. §102(e).



4. An antigen-containing cell genetically modified to express one cytokine, admixed with a second cell genetically modified to express another cytokine (col. 11, lines 34-38). Either cytokine may be a cell-surface cytokine, but, again, Hiserodt only teaches endogenous expression by genetic modification; there is no teaching of a cytokine that is attached to the surface of the antigen-containing cell, having been added to it ***exogenously***. Thus, once again, neither this nor any embodiment of Hiserodt anticipates the instantly claimed invention under 35 U.S.C. §102(e).



Thus, in the respective embodiments taught by Hiserodt, either (1) the antigen bearing cell is in combination with soluble (i.e., **NOT** membrane bound) cytokine, or (2) the antigen bearing cell expresses **endogenous** membrane bound cytokine, or (3) the antigen bearing cell is administered with a second cell that expresses **endogenous** cytokine, which may be attached to the second cell and exogenous to the first cell, but which is ***both*** **attached** to ***and*** **exogenous** to **neither** cell. Therefore, none of the Hiserodt vaccine compositions anticipate the claimed method.

Applicant wishes to emphasize that the instant invention represents a major advance in utility over methods that require endogenous expression of cytokine. The latter approach generally requires expression of a foreign protein from an artificially introduced gene. This is fraught with technical problems that complicate its application to, e.g., medically practical therapeutics. Some types of cells are difficult to transfect. In addition, some cell types express inadequate amounts or none of a given protein from a foreign gene (endogenous expression). The present invention overcomes this by providing a novel way to deliver a desired amount of exogenous cytokine in a potent form.

The Examiner's Answer to Applicant's Appeal Brief asserts that the term "exogenous" as used in the claims "carries little patentable weight in the absence of evidence of structural difference (sic)". The Examiner provides no basis for this assertion; that is, the Examiner is ignoring an express limitation of the claimed invention without providing any legal support or basis for doing so. The law is clear that a **claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference**. See, e.g., *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987). The Examiner asserts that "it is clear that both the prior art and the claimed method administered the same treatment i.e. cytokine coated cells." This is simply not correct. The claimed invention expressly requires that the cytokine coated cells comprise an exogenous cytokine. The Examiner cannot merely ignore this limitation on the claimed invention and conclude that the claimed invention and the prior art are the same. See e.g., *In re Schreiber*, 128 F.3d 1473, 1481 (C.A. Fed. 1997) (The **explicit claim limitations** must be considered in determination of anticipation, just as they would be considered in construing the claims for the purpose of determining infringement. They **can not be ignored**.). Hiserodt et al. do not teach a cytokine coated cell wherein the cytokine is exogenous to the cytokine coated cell. Applicants remind the Examiner that a cytokine coated cell is a cell bearing antigen which is modified to comprise a cell surface associated cytokine. The only cell surface associated cytokines taught in Hiserodt et al. are shown in schematics #3 and 4 above. In each of these examples, however, the cell surface associated cytokine is **endogenous**. It is critical to note that Hiserodt et al. teach that "a cytokine is referred to as a "transmembrane" protein if it normally remains stably associated in the membrane *of the cell in which it is produced*" (emphasis added; col. 13, lines 19-21).

Thus, to the extent that Hiserodt teaches expression in an allogenic tumor cell of a transmembrane cytokine, this teaching is restricted to a situation in which the transmembrane cytokine is *endogenous* to the cell to which it is attached. Hiserodt does **not** teach a cell bearing an exogenous membrane bound cytokine, but teaches only an *endogenous* membrane bound cytokine.

While Applicant agrees that, in one embodiment, Hiserodt teaches an antigen bearing cell in combination with exogenous cytokine, **this is not a cytokine-coated cell.** The exogenous cytokine is secreted by another cell in the vaccine and thus the antigen bearing cell is not modified to bear a cell surface associated cytokine to yield a cytokine coated cell, because Hiserodt et al. do not teach secreting a cytokine which is capable of associating with the cell membrane of an antigen bearing cell. Accordingly, Applicants submit that despite the various vaccine compositions taught by Hiserodt, there is no teaching of a vaccine composition in which a cytokine coated cell wherein the cytokine is exogenous to the cell is administered to a mammal to vaccinate the mammal. Evaluating the claimed invention on an element by element basis, the only conclusion that can be reached is that Hiserodt et al. do not teach each and every element of the claimed invention (either expressly or inherently); mere "substantial identity" is not legally sufficient ground on which to base an anticipation rejection. See, e.g., *Key Pharmaceuticals v. Hercon Laboratories Corp.*, 161 F.3d 709 (Fed. Cir. 1998).

The Examiner asserts that the patentability of the claimed method "does not depend on [the] source of cytokine to produce a cytokine-coated cells (sic) in the absence of evidence of structural difference." To the contrary, the patentability of the claimed method does depend on the source of the cytokine when the source of the cytokine is an express limitation of the claim. The Examiner is not free to dismiss express claim elements in order to find anticipation; each element of the claim must be taught by the prior art. With respect to the asserted lack of structural differences between the cytokines of Hiserodt et al., Applicant nevertheless respectfully disagrees with the Examiner.

The term "exogenous" does, in fact, embody a structural distinction over Hiserodt et al. Specifically, all cells taught by Hiserodt that have cytokine on their surface **necessarily** comprise

an artificially introduced recombinant nucleic acid molecule encoding the cytokine, since, as shown above, expression is from within the cell. Such a nucleic acid molecule is not a feature of the cells of Applicant's claimed invention, since the cytokine is introduced from outside the cell (i.e., is exogenous to the cell). This structural distinction is not only legally important; it represents, as discussed above, a significant improvement in utility.

Furthermore, as shown above, Hiserodt et al. teach two types of cytokines: those that are secreted from the cell, and those that are expressed from the cell and targeted to the cell membrane from within the cell via a transmembrane domain. The present invention requires a cytokine coated cell, defined to be a cell "modified...to bear a cell-surface associated cytokine" (page 4, lines 12-13), and requires that the cytokine be exogenous; that is, a cytokine that is "introduced from or produced outside the cell" (page 10, lines 28-29). The secreted cytokines of Hiserodt et al. are soluble cytokines (col.7, lines 21-26; col. 11, lines 30-34) which do not bind to the cell surface, and are thus necessarily structurally different from the exogenous cytokines recited in the instant claims which, by definition, do associate with the surface of a cell to yield a cytokine coated cell. The transmembrane cytokines (that is, endogenous cytokines which remain associated with the cell membrane of the cell in which they were produced (col. 13, lines 19-23)) taught by Hiserodt et al. are likewise structurally dissimilar from the exogenous cytokines recited in the instant claims, since the former have hydrophobic amino acid sequences that traffic to and reside in the plasma membrane. It is well understood in the art that in order to express a protein on the cell surface, the protein must include specific elements which direct it to the cell membrane, such as a signal sequence, and stop and start transfer peptide binding sites. (See, e.g., Kendrew, The Encyclopedia of Molecular Biology, 1994, Blackwell Science, Ltd., Cambridge, MA (pages 439-444); Alberts et al., Molecular Biology of the Cell, 3rd ed., 1994, Garland Publishing, Inc., N.Y. (Chapter 13)). Thus, the endogenous tumor cell transmembrane cytokines taught by Hiserodt et al. may have vast structural differences compared to the exogenous cytokines of the invention. Applicant reiterates, however, that the presence of structural differences between the cytokines of Hiserodt et al. and the claimed invention is irrelevant, because the instant claims require a cell modified to bear an exogenous, cell surface associated cytokine, and Hiserodt et al do not teach (either actually or inherently) such a cell, and therefore

do not teach each element of the claimed invention, and therefore do not anticipate the claimed invention.

The Examiner also asserts that claims 22 and 25 (dependent claims reciting that the cytokine has various levels of bioactivity, and that the cytokine coated cell is unable to divide in vitro, respectively) are anticipated because the limitations are inherent over the prior art because "it is clear that the prior art and the claimed invention administer the same treatment to achieve the same results". The Examiner asserts (citing MPEP 2112.02) that under the principles of inherency,

> "if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process."

Applicant submits that, as shown above, the method claimed in the base claims (1 or 13) from which claims 22 and 25 depend, and the alleged prior art method are distinct in both method *per se* and in the structural nature of the compositions employed. That is, Hiserodt et al. do not teach the claimed method of claims 1 or 13, and thus the teaching of the additional elements recited in claims 22 and 25, whether express or inherent, is irrelevant. Hiserodt et al. do not teach a method of stimulating an immune response by administering a cytokine coated cell comprising antigen and also bearing an exogenous cytokine. Therefore, Hiserodt et al. do not teach such a method wherein the cell is substantially unable to divide *in vitro* or wherein the cytokine is extremely bioactive, natively bioactive, or suprabioactive.

Taken together, the amendments to the claims and the foregoing remarks distinguish clearly the claimed invention over the teachings of Hiserodt et al. The instant claims are both novel and non-obvious over Hiserodt et al, and Applicant accordingly requests that the rejection be reconsidered and withdrawn.

Rejection of Claims 3-8 and 20 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 3-8 and 20 under 35 U.S.C. §103 as being obvious over Hiserodt et al. in view of a "Known fact" disclosed in Applicant's specification on pages 52-54 and 66-68. The Examiner asserts that Hiserodt's teachings are deficient with respect to claims 3-8 and 20 in that Hiserodt does not teach the specific types of engineered cytokine or specific opsonin-enhanced cells as recited in these claims. The Examiner asserts, however, that the "Known fact" disclosed in the specification teaches that it is conventional and within the skill of the art to produce (i) an opsonin-enhanced cell, wherein the opsonin of the cell is mannose binding protein or alpha' chain of C3b to allow more efficient binding, engulfment and internalization of the antigen; (ii) an engineered cytokine by attaching a lipid to the cytokine to permit a complex to become stably associated with the cell membrane. Applicant respectfully disagrees with the Examiner.

To establish a *prima facie* case of obviousness, several basic criteria must be met. Most relevant to the present case is the requirement that (1) the prior art reference (or references when combined) must teach or suggest *all the claim limitations* (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)). Applicant submits that the teachings of Hiserodt et al., even if combined with the "known fact" asserted by the Examiner, do not teach or suggest all the limitations of claims 3-8 and 20.

As described above, Hiserodt et al. do not teach the base method (claims 1 and 13) from which claims 3-8 and 20 depend. Thus, even if one of skill in the art were to combine the methods taught by Hiserodt et al. with the knowledge in the art that the technology existed to link a lipid moiety to a cytokine molecule, or to employ an opsonin to enhance binding and engulfment, the resulting combination would not include each element of the claimed invention. The Examiner has thus not established a *prima facie* case for maintaining the obviousness rejection over the instant claims.

Moreover, Applicant submits that the "Known fact" referred to by the Examiner, that such an engineered cytokine could be used according to the methods of the invention to stimulate an immune response to an antigen, and that the composition may be combined with an opsonin is a teaching which is unique to the present specification. The combination of a cytokine coated

cell and an opsonin, as claimed in the invention, is not a "known fact". It is the combination on which the invention is based; administration of cytokine-coated cells bearing an exogenous cytokine had never existed prior to the instant invention. The law is clear that taking the teachings of the present invention relating to the claimed method and attempting to fill in the gaps in the prior art with such teachings amounts to hindsight reconstruction of the invention, and is not permitted. Applicant submits that to establish a *prima facie* case of obviousness (in addition to showing that the combination teaches all the elements of the claimed invention) the motivation to combine the "Known fact" with Applicant's novel teachings of a cytokine coated cell, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" (emphasis added) *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). It would not be obvious to one of skill in the art to combine an opsonin with the exogenous cytokine coated cells of the invention, when stimulation of an immune response with the cytokine coated cells of the invention had never been described outside of the present application. The motivation to combine the references cited by the Examiner is gleaned only from Applicant's own disclosure of the invention, and is thus an impermissible hindsight reconstruction of the claimed invention (*In re McLaughlin*, 443 F.2d 1392 (CCPA 1971)). Applicant submits that since, as described above with respect to the traversed rejection under 35 U.S.C. §102(e), Hiserodt et al. does not teach the claimed invention, the Examiner has not met the burden of demonstrating why one of skill in the art, with no knowledge of Applicant's invention, would have been motivated to make the suggested combination. Without the requisite motivation, there can be no finding of obviousness.

Applicant therefore submits that the present invention is not obvious over Hiserodt in view of Applicant's own disclosure, and request that the rejection be reconsidered and withdrawn.

Conclusion

It is respectfully requested that the rejections be reversed and that the claims be allowed.

Respectfully submitted,

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